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Nutrition as both risk factor and intervention in rheumatic diseases

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Abstract. The purpose of the paper is to provide a review of the effects of nutrition as a risk factor and intervention in the aspect of rheumatic diseases. Using information analysis methods, more than 100 special literature sources have been studied, including evidence based medicine computer databases. The significance of nutrition as a risk factor for the development and outcomes, first of all for rheumatoid arthritis and gout, is proved in large observational studies, systematic reviews and meta-analysis dedicated to both preventive and therapeutic potential as well as to safety of different food products, diets, micronutrients and probiotics, including in connection with associated main risk factors of non-infectious diseases (tobacco smoking, alcohol consumption, increased body mass index). The pathogenetic role of nutrition is considered in the context of its influence on gut microbiota. Necessity of the randomized controlled trials is shown in order to assess the protective potential of different nutritional patterns, as well as the effects of modified Mediterranean diet, some dietary supplements and probiotics intake in rheumatic diseases, and as a result — to develop special guidelines on nutrition in rheumatic patients. There is a sufficient evidence base of preventive counseling of such patients on nutritional issues with the aim of cardiovascular risk reduction.

Keywords: rheumatic diseases; nutrition; risk factor; intervention; review

Effects of nutrition in chronic diseases have always been of great interest. A growing awareness in society of the close connection between nutrition, health and life expectancy is associated with «renaissance» of experimental and clinical studies, increase in the number of scientific and popular science publications on nutrition, gut microbiota and noncommunicable diseases (NCDs), including rheumatic diseases. However, special international guidelines on nutrition in patients with rheumatic diseases are not developed. Trying to influence the prognosis and quality of life, associated with the disease and side effects of pharmacotherapy, many patients resort to complementary and alternative medicine, interest in the effects of different diets and dietary supplements on their diseases' manifestations and outcomes [1-7].

Speaking on pathogenesis of most rheumatic diseases (such as connective tissue diseases (CTDs), spondyloarthritis (SpA), and systemic vasculitis), the environmental factors (chemical, physical, infectious ones, as well as nutrition, tobacco smoking, psycho-emotional stress, alcohol consumption, drug use and microbiota changes) are mainly seen as triggers for realizing the

effects of genetic risk factors for the development of autoimmune disorders [8-13]. Nevertheless, more attention is paid to study of the environmental factors' effects [14-19]. Up to 30-60 % of the risk of developing rheumatoid arthritis (RA) is considered to be related to genetic predisposition, while 40-70 % of this risk seems to be associated with the environmental factors' effects, and the magnitudes of their effects depend on age and gender of the patients [20-21]. Causation with nutrition is more evident for other rheumatic diseases: for example, the association of gout attacks — with eating foods rich in purines, the association of knee osteoarthritis onset — with gaining weight, etc. However, the genetic factors, concomitant diseases and pharmacotherapy, as well as muscle training play an important role in the development of these rheumatic diseases [5, 19].

The trend of the last decades is the use of different dietary supplements, especially those containing vitamins and minerals: in 2000 they were consumed by a half of the US population. It is high prevalence of the rheumatic diseases in the USA (they are diagnosed in every twelfth woman and every twentieth man), that allowed obtaining epidemiological evidence of influence

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of such supplements' intake primarily on the development and outcomes of RA [22-23].

Evidence database of the environmental factors' effects in the rheumatic diseases is grounded on the results of such large observational studies as the Nurses' Health Studies (NHSs), the Sister Study Cohort, the Iowa Women's Health Study (IWHS), the Melbourne Collaborative Cohort Study as well. They provide evidence on foods, ingredients, supplements and diets as risk factors of some NCDs' development and outcomes. According to the principles of evidence based medicine (EBM), a gold standard of evaluating effects of foods, ingredients, supplements and diets as interventions (in rheumatic diseases or in high-risk groups) is conducting randomized controlled trials (RCTs). They are the subtype of interventional, or experimental studies.

The results of the analysis of more than 100 sources of special literature show, that only 15 years ago, the assessment of effects of nutrition in rheumatic diseases on the principles of EBM was limited to observational studies, and so far few results have been obtained in RCTs. According to G. Key et al. (2018), it is due to necessity of «continuous scrupulous description of meals» using special validated questionnaires (such as Food frequency questionnaire, FFQ) followed by stratification of the patients [5].

A toolkit for assessing nutritional effects, tested in a number of NCDs, consists of such scales and indexes as Healthy Eating Index (HEI), Alternative Healthy Eating Index (AHEI-2010), Dietary Inflammatory Index (DII), Mediterranean Diet Score (MDS) as well. Using these above-mentioned tools, the effects of nutrition on the integrated health parameters (mortality, morbidity, etc) are evaluated and proven in epidemiological studies. The association of various dietary patterns with the risk of development and other outcomes is proven first of all for cardiovascular disease (CVD) and some forms of cancer [1, 24]. The evidence of association between chronic inflammation in rheumatic diseases and increased cardiovascular risk received in the last decade [25-26] has allowed proposing a hypothesis about therapeutic and preventive effect of various diets, foods, ingredients and dietary supplements.

Today, the trigger potential of diets, foods, ingredients and supplements is best studied in RA. Some contribution to this knowledge was made by the results of the US nursing cohort studies Nurses' Health Studies (NHS, NHS II, NHS III) received in 1976-2016 [20, 27-32]. They provide evidence of strong inverse correlation between duration of breastfeeding lasting ≥ 12 months in infant girls and probability of RA development in their adulthood. These studies' results have also proven a number of effects of smoking, coffee and alcohol consumption in terms of the developing RA, systemic lupus erythematosus (SLE), etc. Lack of breastfeeding in infancy is also associated with an increased

risk of SpA development, but evidence of this effect is weaker than for RA [5].

In 2013, C.G. Parks et al. [33] published the results of the Sister Study Cohort initiated by the National Institute of Environmental Health Sciences and included more than 50000 white women-residents of the USA aged 35-74. These results confirmed significant (50 %) increase in risk of developing RA related to low birth weight, unsafe nutrition (malnutrition) in childhood, low quality of home education and generally low socioeconomic status. However, no foods were identified as risk factors for developing RA.

Recently, based on the 11 nutrients' and foods' proven effects on the risk of developing major NCDs (CVD, some types of cancer, diabetes mellitus (DM) type 2) the index of nutrition quality AHEI-2010 has been developed. Healthy nutrition means use of vegetables, fruits, nuts, whole grain products, polyunsaturated fatty acids (PUFAs), omega-3 PUFAs and moderate alcohol consumption, while the components of unhealthy nutrition are sweet soft drinks (including sweet fruit juices), saturated fats, trans fats, salt, red and processed meat.

In 2017, noting the lack of studies on the effect of dietary quality on the autoimmune diseases' development, Y. Hu et al. [20] evaluated the association between AHEI-2010 with the risk of RA. It was first established that low quality of nutrition (low score AHEI-2010, unhealthy nutrition) is risk factor for developing this disease. The source of evidence was the prospective comparative study of two female cohorts: NHS (n=76597) and NHSII (n=93392) aged respectively 30-55 and 25-42 at baseline and free from RA or other CTD. The lifestyle, environmental exposure and anthropometric information were collected at baseline and updated biennially. The primary outcome was RA alone and its two subtypes — seropositive and seronegative RA. During the conducting of the study, 1007 RA cases were confirmed. Among women aged ≤ 55 years «better quality diet» was associated with lower RA risk: comparing Q4 vs Q1, hazard ratio (HR) was 0,67, 95 % confidence interval (95 % CI) 0,51-0,86. This inverse association was even stronger for seropositive RA (HR=0,60; 95 % CI 0,42-0,86). No significant association between quality of nutrition and risk of RA was found for women aged > 55 . The authors concluded, that less healthier diet is associated with increased risk of RA (particularly seropositive RA) occurring in women aged ≤ 55 years.

Negative health effects of taking the popular in the USA dietary vitamin and mineral supplements reflected the results of the IWHS (1986-2008). The participants of this observational study were 38772 women whose mean age at baseline was 61,6 years. During the study period, supplement use was self-reported three times. It turned out that in 1986 at least one supplement was taken daily by 63 % of the respondents, in 1997 — by 75 %, in 2004 — by 85 %; moreover, 27 % of women took daily

≥4 supplements. 40,2 % of the participants (n=15594) died over the entire observation period.

Analysis of the IWHs results has shown the association between taking of multivitamin supplements and increased risk of total mortality when compared with corresponding nonusers. As can be seen from the table 1, the effect of using copper-containing supplements turned out to be especially significant: the absolute risk increase for all-cause death reached 18 %. According to J. Mursu et al. (2011) [22], «the most probable» was negative effect of the additional use of iron, while adding of calcium was associated with reduced risk of all-cause death: HR=0,91 (95 % CI 0,88-0,94), absolute risk reduction — 3,8 %.

The authors noted, that in the USA namely older women remained main users of vitamin and mineral supplements, which are clearly benefit in the face of deficiency conditions. They also indicated the following: 1) heterogeneity of the evidence, including meta-analysis of L. Bazzano et al. (2006) and G. Bjelakovic et al. (2007); 2) concentration of the RCTs mainly on effects of vitamins B, C, D, E and calcium (harm, or no such benefit as reduction of risk of death); 3) necessity of further studies of health effects of long-term use of supplements containing multivitamins, iron and other microelements as well.

Smoking. It is worth emphasizing that all studies on effects of nutrition as risk factor or intervention in the rheumatic disease should take into account the participants' status of smoking. The results of the analysis of the present evidence allow to consider a complete cessation of smoking the most effective technology of primary prevention of RA (namely of its unfavorable subtype — seropositive RA) [5, 30, 34-36]. In accordance with the terminology given by the Center for Disease Control and Prevention (www.cdc.gov/nchs/nhis/tobacco/tobacco_glossary.htm; accessed at: 07.07.2019), ever smoker is a person who has smoked at least 100 cigarettes in his or her life. The biological effects of short «social» smoking are questionable.

In 2014, D. di Giuseppe et al. [36] studied the association between exposure to cigarette smoking and risk

of RA — in the meta-analysis of 10 observational studies, selected in the computer databases MEDLINE and EMBASE from publications of 1966-2013. The meta-analysis of 3 prospective cohort studies and 7 retrospective «case-control» studies (a total of 4552 cases of RA) has proved an increased risk of RA in smokers when compared with never smokers: 26 % increase in smoking index 1-10 pack-years (relative risk (RR) 1,26; 95 % CI 1,14-1,39) and double increase in smoking index >20. In smoking index 21-30 pack-years RR of RA development was 1,94 (95 % CI 1,65-2,27), in smoking index >40 — 2,07 (95 % CI 1,15-3,73). Regardless of smoking index, increased risk of developing RA, which is rheumatoid factor (RF) seropositive, was higher (RR=2,47; 95 % CI 2,02-3,73), than increased risk of developing RF-seronegative RA (RR=1,58; 95 % CI 1,15-2,18). So, it turned out that even a slight exposure to cigarette smoking increases the risk of RA developing during the lifetime; this risk is maximum (2 times higher than in never smokers) in smoking index >20 pack-years, and further increase in dose does not affect the effect.

Already in 2019 X. Liu et al. [30] represented their analysis of the data from the Nurses' Health Studies. They have proven the following:

1) female-smokers when compared with never smokers have 47 % increased risk of developing RA (HR=1,47; 95 % CI 1,27-1,72), particularly of seropositive subtype (i.e. of higher disease activity, severe articular destructions and extra-articular manifestations) — 67% increased risk (HR=1,67; 95 % CI 1,38-2,01);

2) duration of smoking cessation period is favorable risk factor in terms of risk of developing RA, and first of all of its seropositive subtype: those former smokers who quit smoking long ago (>30 years) have a 37% lower risk of developing seropositive RA (HR=0,63; 95 % CI 0,44-0,90) than those who quit smoking in the last 5 years. Nevertheless, when compared with never smokers, the former smokers who quit smoking long ago (>30 years) have «moderately increased» risks of developing both RA (HR=1,25; 95 % CI 1,02-1,53) and seropositive subtype of the disease (HR=1,30; 95 % CI 1,01-1,68);

Table 1. Effect of use of dietary supplements on the risk of all-cause death in older women (according to the Iowa Women's Health Study [22])

Component of dietary supplement (vitamin, microelement)	Effect of use of supplement in comparison with no use	
	Risk of all-cause death (hazard ratio; 95 % CI)	Absolute risk increase, %
Multivitamins	1,6 (1,02–1,10)	2,4
Vitamin B6	1,10 (1,01–1,21)	4,1
Folic acid	1,15 (1,00–1,32)	5,9
Iron	1,10 (1,03–1,17)	3,9
Magnesium	1,08 (1,01–1,15)	3,6
Zinc	1,08 (1,01–1,15)	3,0
Copper	1,45 (1,20–1,75)	18,0

CI – confidence interval.

3) it is «only the trend» proven for the association between duration of smoking in the past and increased risk of RA developing;

4) unlike the results of meta-analysis of D. di Giuseppe et al. (2014), the effect of smoking on risk of developing seronegative RA has not been confirmed in this study (HR=1,20; 95 % CI 0,93-1,55).

So, following the establishment of a dose-dependent (cumulative) effect of smoking as a risk factor of RA development in genetically predisposed individuals, it was recently first proven a positive preventive effect of behavior changes, namely of prolonged (>10 years) sustained tobacco cessation regarding reducing the risk of developing this disease. The source of evidence was 38 year observation of female cohort — a total amount of 230732 US residents, including 1528 who developed RA (seropositive subtype in 63,4 % of cases). The authors of the publications themselves criticize the validity of the study — both external (i.e. the ability to extrapolate its results to the general population, taking into account the biased sample of «predominantly well-educated white women») and internal one (since the intervals for assessing smoking status were at least 2 years). The evidence of effect of smoking cessation on the outcomes in patients with established diagnosis of RA remains weak: by stopping smoking, patients can reduce the risks posed by the disease [30].

Now then, so far as smoking is a strong risk factor of developing seropositive RA, the planning, conducting and assessing results of the studies dedicated to the effects of nutrition with this disease should consider smoking as a confounding factor, like with other NCDs (lung cancer, etc.).

Coffee. Several studies on the influence of nutritional and other external factors on the outcomes with RA have been already conducted considering status of smoking. The example is the study on the effects of alcohol consumption carried out by H. Kallberg et al. (2009) [34]. Smoking as a compounding factor was also taken into account in one of the first studies on the effects of coffee intake conducted by M. Heliövaara et al. (2000) [37]. In this cross sectional survey of 6809 subjects without RA in the past and at the baseline, the association between the RF titre and the number of cups of coffee drunk daily has been studied. Multivariate analysis revealed the association between coffee intake and the risk of developing RF-seropositive RA: the users of ≥ 4 cups of coffee a day had a relative risk of 2,2 (95 % CI 1,13-4,27) compared with those drinking less. This effect of coffee has been proven in the cohort of men and women (n=18981) included in the survey in 1973-1976; in 1989, the diagnosis of RA was established in 126 (0,7 %), the proportion of RF-seropositive disease was 70,6 %.

In 2002-2003 two more articles were published that presented the results of the studies on the influence of coffee, *decaffeinated coffee, tea and caffeine* on the

risk of developing RA conducted in the USA. The aim of the study of T.R. Mikuls et al. (2002) [38] was to assess the effects of coffee, tea and caffeine as potential risk factors of developing RA in older women. This prospective cohort study started in 1986 and included 31336 women aged 55-69 years without RA in their past; after 10 years the diagnosis of RA was established in 0,5 % of the participants (n=158). The results of the study shown more than twice the risk of developing RA when consumed ≥ 4 cups of decaffeinated coffee a day compared with no use (RR=2,58; 95 % CI 1,63-4,06). Women who drank >3 cups of tea a day had lower risk of developing RA compared to those who did not drink tea (RR=0,39; 95 % CI 0,16-0,97). The influence of both coffee and caffeine on the developing of RA has not been proven. These results were confirmed by the multivariate analysis, which took into account the age, age of menopause, status of smoking, of alcohol intake, of hormone replacement therapy and marital status as well. The association between the increased risk of the late onset of RA with high consumption of both decaffeinated coffee (RR=3,10; 95 % CI 1,75-5,48) and tea (RR=0,24; 95 % CI 0,06-0,98) turned out to be stronger in women with seropositive RA (RR=1,54; 95 % CI 0,62-3,84) compared to those with seronegative RA (RR=0,93; 95 % CI 0,27-3,20). The authors concluded that in postmenopausal women drinking decaffeinated coffee is a risk factor for developing RA, but tea consumption is associated with a reduction in this risk.

In 2003, the representatives of the Harvard Medical School E.W. Karlson et al. [32] published their results on the effects of these drinks (coffee, decaffeinated coffee, tea) and caffeine as risk factors of developing RA — according to the results of the NHS 1980-1998. At first, the studied cohort included 121701 women, but the primary questionnaire FFQ was filled out correctly only by 68,3 % of them (n=83124), and subsequently they were interviewed every 4 years. During 20 years the diagnosis of RA was established in 0,58 % of cases (n=480). The results shown no significant association between high coffee consumption (≥ 4 cups a day) — both caffeine-containing and decaffeinated coffee — and the incidence rate of RA, as well as no cumulative effect of high coffee or tea consumption (>3 cups a day) on the risk of developing RA when compared with no use of these drinks: RR=1,1 (95 % CI 0,8-1,6) and RR=1,1 (95 % CI 0,7-1,8) respectively. Also, there was no association between the total consumption of coffee and caffeine and the increased risk of developing RA.

So, the effects of coffee, decaffeinated coffee, tea and caffeine consumption regarding the risk of developing RA were assessed in 2000-2003 in three observational studies conducted in Finland and the USA, lasted for 10-20 years and included more than 133 thousand participants, mostly women. Their results turned out to be heterogeneous.

Alcohol. The information analysis has shown that in those who are genetically predisposed to RA, the low to moderate alcohol intake (i.e. 1-5 doses per week) greatly reduces this risk [34], namely the risk of developing seropositive RA [27, 39] and it is in women [14, 27]. When consuming alcohol in an amount >10 g/day (in terms of pure alcohol), its protective effect disappears [27].

Note, that in accordance with the recommendations of the Center for Disease Control and Prevention (www.cdc.gov/alcohol/fact-sheets/alcohol-use.htm; accessed at: 07.07.2019) and the World Health Organisation (www.euro.who.int/ru/health-topic/disease-prevention/alcohol-use/do-you-drink-too-much-test-your-own-alcohol-consumption-with-the-audit-test; accessed at: 07.07.2019), a standard dose (a portion or unit) is considered 10 g of pure alcohol. «Very low» consumption means consuming alcohol in an amount less than a dose a week, «moderate» — up to 1 dose a day for non-pregnant women and up to 2 dose a day for men aged ≥ 21 years, when implying not every day drinking. The dose of alcohol is contained in 425 ml of 2,7 % beer, 285 ml of 4,8 % beer, 100 ml of champagne or 13 % wine, 60 ml of 20 % wine, 30 ml of 40 % distilled spirits or liquor (examples: gin, rum, vodka, whiskey). In the USA, a dose of alcohol (a «drink») is considered 12 ounces of 5 % beer (354 ml), 8 ounces of 7 % malt liquor (237 ml), 5 ounces of 12 % wine (148 ml), 1,5 % ounces of 40 % distilled spirits or liquor (44,4 мл).

In 2009, H. Kallberg et al. [34], knowing the results of two «case-control» studies — the EIRA and the CACORA, established the association between the risk of developing RA and the use of alcohol, when considering both smoking status and genetic factor (HLA-DRB1 gene carriage). The EIRA was conducted in Sweden and included 1204 «cases» and 871 «controls»; the CACORA was carried out in Denmark, its participants were 444 patients with RA and 533 control subjects. As a result, much higher prevalence of alcohol use in the control groups than among patients has been revealed; H. Kallberg et al. have also shown a dose-dependent effect of alcohol use regarding a decrease of the risk of developing RA — in the both mentioned studies. The consumers of «the largest amounts» of alcohol have shown better outcomes (i.e. lower risk of developing RA) when compared to the consumers of «the smallest amounts»: the RR in the EIRA was 0,5 (95 % CI 0,4-0,6), in the CACORA — 0,6 (95 % CI 0,4-0,9). It has been shown the association between the alcohol intake and the decreased risk of developing RA, which was seropositive for antibodies to cyclic citrullinated peptide (ACCP), mainly in the HLA-DRB1-positive smokers.

Based on the established inverse association between the alcohol intake and the risk of developing RA, and taking into account the results of the experimental research, the author suggested a protective effect of alcohol regarding the risk of developing RA and concluded

the lifestyle factors' importance (smoking cessation, but not necessarily alcohol) for reducing the risk of developing this disease.

After 4 years, the hypothesis of H. Kallberg et al. was supported by the results of the systematic review of I.C. Scott et al. [39] that revealed an inverse association between the alcohol intake and the risk of developing ACCP-positive RA. The aim of this review and the meta-analysis was to assess the effect of alcohol consumption regarding the risk of developing RA when considered its amount and duration, and ACCP-status as well. The search of primary evidence has been in the MEDLINE and the EMBASE performed taking into account data from 1946 till July 2012. As a result, 9 observational studies have been selected, including 6 «case-control» studies (a total number of participants was 3564 cases and 8477 controls) and 3 cohort studies (444 patients in the main groups, 84421 in the control ones). As for the risk of developing RA, the odds ratio in the users of alcohol when compared to non-users was 0,78 (95 % CI 0,63-0,96). This effect was observed only with ACCP-seropositive subtype of RA (OR=0,52; 95 % CI 0,36-0,76), while the influence of alcohol intake on the risk of developing seronegative RA was not confirmed (OR=0,74; 95 % CI 0,53-1,05). The authors considered it necessary to strengthen the evidence of the protective role of alcohol intake to reduce the risk of developing RA by conducting prospective studies of the ACCP-positive cohorts.

Using such a source as two large prospective cohorts from the NHSs, B. Lu et al. (2014) [27] evaluated the risk of developing RA regarding the alcohol intake in women. The NHS started in 1976 included 121701 participants, while the NHSII started in 1989 included 116430 ones. It was the interviewing them every 2 years that allowed to establish the effects of several environmental and lifestyle factors. To assess the effects of alcohol intake, the women were interviewed every 4 years with the FFQ questionnaire. In 2008-2009, the number of the patients with RA turned out to be 580 in the NHS's cohort, 323 in the NHSII's cohort. When drinking alcohol in quantities 5,0-9,9 g/day, the HR of developing RA was 0,78 (95 % CI 0,61-1,00), a stronger association was proven with seropositive RA (HR=0,69; 95 % CI 0,50-0,95). Besides, the beneficial effect of **beer** consumption has been revealed: women who consumed beer 2-4 times a week has a 31 % lower risk of developing RA than those who did not drink beer. Having established a «modest association between long-term moderate alcohol drinking and reduced risk of RA», B. Lu et al. considered it necessary to strengthen the evidence of their conclusion.

In the same year, Z. Jin et al. [14] published the meta-analysis of 8 prospective studies on effect of alcohol consumption on the risk of developing RA. Its statistical power is reflected in the total amount of participants — 195029, including 1878 patients with RA. Protective ef-

fect on RA development has been proven for low and moderate alcohol consumption (RR=0,86; 95 % CI 0,78-0,94), however, the dependence of the effect on the dose was not linear. Compared to not drinking alcohol, RR of developing RA at its use in a dose 3 g/day was 0,93 (95 % CI 0,88-0,98), for 9 g/day — 0,86 (95 % CI 0,76-0,97), for 12 g/day — 0,88 (95% CI 0,78-0,99), for 15 g/day — 0,91 (95 % CI 0,81-1,03), for 30 g/day — 1,28 (95 % CI 0,94-1,73). The analysis in the subgroups revealed a decrease in the risk of developing RA by 19 % in women who consumed alcohol in low and moderate doses. Regardless of gender, prolonged (for 10 years and more) constant use of alcohol in such quantities reduced the risk of developing RA by 17 %. The authors' conclusion was to confirm both a protective effect of low and moderate alcohol consumption regarding the risk of developing RA and a dependence of this effect on dose and duration of alcohol use and gender of patients. According to Z. Jin et al., studying effects of the «interactions of genes and environmental factors» in large prospective studies opens up the prospect of establishing the etiology of RA.

In general, according to G.D. Kitas et al. (2011) [25], the prophylactic efficacy of moderate alcohol use is to reduce the risk of developing and the incidence rate of seropositive RA, and the therapeutic one — to slightly decrease the activity of RA. Moreover, M.J. Nissen et al. (2010) [40] observed a slowdown in the progression of articular destruction in male RA patients who consumed alcohol in an amount of ≤ 1 dose/day for 4 years; at the same time, alcohol abuse increased disease activity.

As noted above, the inverse association between moderate alcohol intake and risk of developing disease was established in the NHSs' cohorts not only with RA, but also with SLE; that can be explained by anti-inflammatory properties of such doses of alcohol. M. Barbhuiya et al. (2017) [29] presented the results of the prospective observation of 204055 participants in the NHS (during the period 1980-2012) and the NHSII (1989-2011) who were free of CTD and provided information on alcohol intake (including beer, wine, and liquor) at baseline. Later they reported such data, filling out semiquantitative questionnaire every 2-4 years. Incidence of SLE in both cohorts was 0,12 % (125 incident SLE cases developed in women of age $55,8 \pm 9,5$ years, and 119 cases — at the age of $43,4 \pm 7,7$ years). The results shown a significant reduction of the risk of developing SLE when drinking alcohol (for cumulative average alcohol intake ≥ 5 mg or 0,5 dose daily), compared to no alcohol intake (HR=0,61, 95 % CI 0,41-0,91). Women who drank ≥ 2 servings/week of wine had significantly lower SLE risk (HR=0,65; 95 % CI 0,45-0,96), compared to women who did not drink wine.

We also note the association between the increased risk of developing RA and the intake of **high fructose drinks** at a young age revealed by L.R. DeChristopher

et al. (2016) [41] in the cohort study of 20-30-year old Americans.

Body mass index (BMI), like smoking, is studied as a factor associated with nutrition (and possibly a confounding factor, too) in terms of the development and outcomes of certain rheumatic diseases.

A number of advantages have overweight RA patients (i.e. BMI 25-30 kg/m²), which G. Keyßer (2018) [5] called «optimal» for this disease. First of all, in the debut of RA overweight is associated with the probability of achieving remission and slowing down the progression of articular destruction [42]; secondly, the risk of developing CVD in overweight RA patients is lower than in underweight patients [25]. Nevertheless, obesity (i.e. BMI ≥ 30 kg/m²) is a risk factor for developing RA [7]; obese RA patients have higher disease activity, greater joint pain and more associated diseases [43]. As for effects of underweight, rheumatoid sarcopenia, rheumatoid cachexia, and metabolic syndrome, nowadays they are subjects of a number observational studies [16].

Nutritional and nutrition-related risk factors of developing RA in smokers. RA in smokers is more common and more severe than in non-smokers [5, 35]. Significant additional risk of developing RA in smokers is associated with some nutritional factors, especially with **sodium chloride** intake. In 2015, B. Sundstrom et al. [44], based on the «case—control» study's results, established more than twice increased risk for RA among smokers, who consumed sodium in a dose 5,5 g/day, compared with smokers who consumed sodium in a dose 3,8 g/day, and revealed an association between this effect and the duration of smoking. It remains a question whether sodium is an independent (and a confounding) risk factor for RA, or whether the risk increase is associated with the use of certain salt-containing foods.

Increased BMI in smokers is associated with a reduction of risk of developing RA, while in non-smokers — with significant risk increase. In 2013, the cohort of smokers was studied by M.J. de Hair et al. [45]: it turned out that the cumulative risk of developing RA during 2-3 years in overweight subjects is 70 % higher than that of persons with BMI < 25 kg/m².

We also note that smoking, along with dietary pattern, drug intake and stress as well, belongs to the factors affecting gut microbiome.

Meat, fish, preferred food and risk of RA. Despite the common concept of the association between intake of red meat (beef, pork, fowl) and developing RA, the information analysis confirms weakness of evidence for this statement.

In the above-mentioned study on the association between the AHEI-2010 and the incidence of RA, red meat was not considered as independent risk factor, but as a «component of unhealthy diet which increases risk of developing RA» [20]. Little evidence of the direct effect of red meat intake is found in the literature, and this effect was «weak» and «uncertain» in the cohort studies

of 26 and 80 thousand patients respectively [46-47]. It is important that the second of them — the NHS' participants — had reported on their dietary habits regularly for more than 20 years.

As for fish consumption, 15 years ago D.J. Pattison et al. (2004) [46] noted homogeneity and consistency of evidence of beneficial effect of fish oil intake on the severity of RA symptoms, as well as no evidence of influence of PUFAs contained in fish oil on the risk of developing this disease. They indicated both a less severe course of RA in Italy and Greece with their much higher consumption of fatty fish, fruits, vegetables and olive oil than in many other countries, and the association between the increased incidence of RA in the Norfolk (England) with its low consumption of vegetables, fruits and vitamin C.

Currently, the evidence base for reducing the risk of developing RA due to the consumption of fatty fish is considered weak [5]. Moreover, the increased intake of leaner fish is associated with an increase of this risk. First it was established by M. Pedersen et al. (2005) [48] with the results of the 5-year prospective cohort study of 57 thousand patients who filled out the special FFQ questionnaire. The outcomes were compared with data from the Danish national patient register, and it turned out that 69 participants of the study (0,12 %) had RA. An important outcome of this study is to establish a reduction in the risk of developing RA by 49 % when eating 30 g/day of fish oil (as part of fatty fish containing fat in the amount of ≥ 8 g/100 g) and significantly increasing the risk of developing RA when eating less fatty fish (containing fat in the amount of 3-7 g/100 g). No association was detected between the risk of developing RA and consumption of fruits, coffee, olive oil, meat, long-chain fatty acids, iron, zinc, selenium, vitamins A, E, C, D as well. The authors indicated that it was a small number of participants of this large cohort study, who developed RA, kept them from a low appreciation of the role of food factors in the development of this disease. They promoted a hypothesis of an influence of earlier (or longer period of) certain food components' consumption on the risk of developing RA and of a necessity of longer follow-up respectively.

So, according to modern concepts, the environmental factors are important in the development of RA. Until recently, smoking was the only certain strong risk factor for the development of RA (namely for its prognostically unfavorable ACCP-seropositive subtype in carriers of a particular genotype). However, the effect of both alcohol and coffee intake on the risk of developing RA has been proven by the evidence from some cohort studies. Our information analysis shows that the benefit and harm of the other foods, nutritional components, habits, diets and dietary supplements regarding the risks connected with RA have also been studied and discussed everywhere constantly over the past 40 years [4-5, 49-52].

In China they were studied by J. He et al. [52], who presented in 2016 the results of the multicentre retrospective case-control study on association between «preferred consumption» of the certain foods and the rate of incidence of RA. More than 2 thousand participants were enrolled from May 2012 to September 2013, including 968 patients with RA. The control group comparable to the group of «cases» by ethnicity, region of residence, average age and gender distribution included 1037 healthy persons. The interviewing of the participants allowed to collect detailed information on their food preference during the 5 years preceding the onset of RA (in the group of «cases») or the enrollment (in the control group): «Did you use the products from this list during the week, and if so, in what quantity». The list included red meat, poultry, fish, offal, vegetables, potato, beans, nuts, mushrooms, milk and dairy, eggs, fruits, citrus, etc. The results shown that for 5 years before the onset the patients with RA ate much less fish, poultry, beans, citrus fruits, dairy, mushrooms and offal than the healthy persons.

Based on the results of the multivariate analysis, such risk factors of RA have been established in the Chinese cohort: female gender (OR=2,4) and age >50 years (OR=3,4 for 51-60-year-olds, OR=5,5 for 61-70-year-olds, OR=3,8 for people aged 71 and older), and a direct association of potato and fruits (except citrus) consumption and RA incidence. The reduced risk of developing RA was associated with the increased intake of mushrooms, dairy and citrus fruits as well. As for red meat and vegetables, there was no association between their consumption and RA incidence revealed in this sample; the expected protective effect of increased use of fish and beans also was not confirmed (although there was a tendency).

Considering the much lower red meat consumption in China when compared to the developed Western countries, J. He et. [52] have noted the need to further study the effects of this nutritional factor in the prospective studies. The important results of this study is putting forward a scientific hypothesis about the association of the development of RA with certain dietary habits (addictions).

Lack of consistent evidence of both a protective effect of certain nutrients and products (high doses of alcohol, fish, unrefined olive oil, steamed vegetables, etc.) and an unfavorable effect of the others (red meat, sweet drinks as well) regarding the risk of developing RA is explained by Hu Y. et al. (2017) [20] that such effects are possible only with the «combined action of several food factors».

Mediterranean diet, its modification and risk of RA.

Mediterranean diet is rich in plant-based foods, vegetables, fruits, wholegrains, fish and seafood and low in meat and dairy products intake. The significant source of fats is extra-virgin olive oil, of carbohydrates — dried fruits and honey. Regardless of favorable metabolic

effect of such nutrition confirmed by the Dietary Intervention Randomized Controlled Trial Group (DIRECT) [53], its effect on the risk of developing RA is not proven [6-7, 54]. Taking into account the popularity of the Mediterranean diet as a technology of primary prevention of RA, it is «lack of evidence in support of this common recommendation» noted in the systematic review of C. Forsyth et al. (2018) [3].

E. Philippou et al. (2018) [7] write about possible association between the development of RA and a «Western» type diet rich in energy intake, total and saturated fat, unbalanced ratio of short- and long-chain fatty acids, high in refined carbohydrates and sugar and low in fiber and antioxidants. This risk increases directly (by maintaining inflammation) and indirectly (by developing insulin resistance and obesity). According to E. Philippou et al., a prophylactic potential of the use of long-chain omega-3 PUFAs — eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) — is related to their anti-inflammatory properties. Based on current research evidence, the scientists suggest association of a reduced risk of developing RA with adherence to the «enhanced» *Mediterranean diet* — with an increased consumption of fatty fish, reduced consumption of sugar-sweetened drinks and maintenance of a normal body weight. According to the authors, further research will allow «more specific nutritional recommendations» for prevention developing RA to be made.

Vitamins and microelements as risk factors of the developing RA. The influence of the additional use (as parts of dietary supplements) of some vitamins and minerals on the incidence of RA has been studied on materials of 2 large studies — an observational study IWHS and an interventional placebo-controlled RCT Women's Health Initiative CaD trial. As a result of the IWHS, it was proven a slight protective effect of zinc supplementation, as well as of additional use of beta cryptoxanthin (a provitamin A containing in citrus fruits, apples, flowers of *Physalis* and a variety of other plant products) [22, 55-56].

The aim of the IWHS was to study an association between internal, nutritional and lifestyle-related factors and the rate of incidence of cancer in older women. After exclusion of those who incorrectly filled out a questionnaire on nutrition and dietary supplements' intake, 38772 participants were subjects for further observation in 1986, 29230 — in 1997, and 19124 — in 2004. In 1997, the only data on the supplements' use (not on the nutrition) were evaluated. The research tool was 2 validated versions of the Harvard FFQ questionnaire, the composition of the food was evaluated using special databases. As a result, effects of 15 supplements were studied, including vitamins A, B6, C, D, E, iron, calcium, selenium, zinc (all with known doses), multivitamins, vitamin B complexes, beta carotene, folic acid, magnesium and copper. Effects of cholecalciferol and ergocalciferol were not separately evaluated. The most

popular were supplements containing calcium, multivitamins, vitamins C, E, as well as complex supplements containing calcium (with multivitamins, vitamins C, multivitamins and vitamins C).

Characterizing consumers of the dietary supplements (the proportion of which among the participants in the IWHS increased in 18 years from 63 to 85 %), J. Mursu et al. (2011) [22] wrote, that at the beginning of the study they were less likely than non-consumers to smoke, to live in the countryside, to suffer on DM and hypertension. They were more educated and physically active, had smaller BMI and waist to hips ratio, more often received hormone replacement therapy as well. Their usual diet was not so rich in energy intake and saturated fat, but contained more proteins, PUFAs, carbohydrates, alcohol, wholegrains, vegetables and fruits. The similar dietary pattern was also observed at the end of the study and separately among the consumers of the iron- and calcium-containing supplements.

Well-known result of the IWHS is confirmation of the hypothesis about lack of beneficial effect of dietary supplements' use on the all-cause mortality in older women. The conclusions of J. Mursu et al. (2011) were, firstly, in establishing the association of the popular vitamin and mineral supplements' use with the increased total mortality. Secondly, additional use of iron turned out to be a strong risk factor of all-cause death in older women, including those who did not have CVD, cancer and DM, and at different stages of the 19-year observation period. It was explained by the fact that an excess of iron catalyzes the reactions, which result in formation of oxidants; besides, it was not excluded the association of increased mortality also with diseases and injuries that led to anemia and the prescription of iron preparations. Third, J. Mursu et al. first proven such an effect of calcium supplementation as reduction of all-cause mortality, but they did not observe the dose-related effect. Earlier, the prospective studies' meta-analysis of L. Wang et al. (2010) revealed a downward trend in cardiovascular risk due to taking vitamin D (HR=0,9; 95 % CI 0,77-1,05), but not calcium (HR=1,14; 95 % CI 0,92-1,41) [22].

Current evidence of the influence of vitamin D supplementation on the incidence rate of RA is inconsistent: the slight protective effect was estimated in one study [57], while the increased incidence rate of RA in case of increased taking of this vitamin and calcium was observed in the others. In 2012, M. Racovan et al. [58] reported the results of the large placebo-controlled RCT on the effect of vitamin D and calcium supplementation on the incidence of RA in the cohort of the Women's Health Initiative CaD trial (n=36282). Women in the main group took daily 1000 mg of calcium carbonate plus 400 IU of vitamin D3. No significant difference in demographics, total personal vitamin D intake, or solar irradiance were seen between the groups. Analyzed were the outcomes in 32435 women free of RA at base-

line; during 5,1 years of observation this diagnosis was established in 163 (0,5 %) of them. As a results, the association of the incidence rate of RA in postmenopausal women with taking supplements containing vitamin D plus calcium was not observed (HR=1,04; 95 % CI 0,76-1,41). M. Racovan et al. recommended further research on the effects (including adverse ones) of taking higher doses of vitamin D for primary prevention of RA.

Dietary interventions in RA patients. According to K. Masuko (2018) [16], use of some diets «may be considered for RA patients because of the high incidence of cardiovascular comorbidity ... and mostly undefined modulating effect» of such interventions.

Along with the other factors, it is important to take into account a distinct gut microbiota in patients with RA, SpA, SLE when compared to healthy subjects, and the fact that the oral microbiota is also changed in Sjögren syndrome [9-13], as well as possible changes of its composition in case of restricted or increased intake of certain nutrients and foods [7, 16].

The Cochrane review and meta-analysis of K.B. Hagen et al. (2009) [59] summarized the results of 14 RCTs on the various diets that 837 RA patients adhered to, and it was concluded that there were «only a few facts» in favor of their effectiveness. Small sample sizes and the studies' designs were criticized. A large number of patients prematurely withdrawn from the studies were regarded by the authors as the result of AE development. Current evidence «did not allow advising» management of the patients with active RA based on diet therapy as an alternative to basic drug therapy. Also noted was the uncertainty of the effect of dietary interventions in RA in the long term.

The studies on nutritional interventions in RA. The aim of the interventional studies in RA is to reveal and evaluate the effect of the nutritional interventions (first of all of the diets) on the disease activity. On the other hand, supplementation of vitamins, minerals and antioxidants can contribute to the achievement of the goal of the treatment — clinical remission/minimal disease activity; so, the effects of these dietary supplements also need to be studied.

Over the past 20 years, a number of studies on the effects of various diets — elementary, elimination (gluten-free, etc.), vegan and vegetarian ones — have been conducted in the cohorts of RA patients [60-63]. Their methodology excludes «blinding» and implies both solid training and high motivation of the patients as well as the selection bias' presence (i.e. predominance in the biased samples of the patients who are inclined to change their nutrition); however, none of such studies has proven a sustained effect of diet on RA activity. Many patients prematurely terminate their participation [62-63], which, according to G. Key et al. (2018) [5], clearly demonstrates the «possibility of a significant reduction in the quality of life ... as a result of intervention in the usual diet».

Analyzing below the presence and magnitude of the effects of various nutritional interventions for RA, established in the interventional studies, we refer to S. Petersson et al. (2018) [6], who have indicated a limited validity of their results due to the complexity of their methodology.

Elementary diets imply food restriction to the use of the simplest components, i.e. glucose, albumin, essential aminoacids, vitamins, etc. Theoretically such food provides elimination of antigens of all foods, which are triggers for arthritis. In 2007, T. Podas et al. [64] evaluated the effect of 2-week elementary diet in RA in their pilot interventional study, but the subjective improvement in the patients (a decreasing pain and morning stiffness) was not persistent.

Elimination diets as interventions and diagnostic tests are used in allergology to eliminate allergy symptoms and identify the food allergen, respectively. Having started a non-allergenic diet, the list of products allowed for intake is gradually expanded, which makes it possible to identify a product that exacerbates RA manifestations. In practice, patients sometimes notice an increase in pain and swelling of the joints after consuming certain products «with high individual variability» — from meat, milk and citrus fruits to coffee and sweets [65-66]. Despite weak evidence on the elimination diets' effects in RA, in many European clinics, doctors are advised to draw the attention of patients to the dependence of RA symptoms on the menu and to avoid the use of appropriate products [5].

Fasting, veganism, lactovegetarianism. 40 years ago L. Sköldstam et al. (1979) [49] conducted a controlled study of the effects of 7-10-day fasting with the transition to 9-week lactovegetarian diet in 16 patients with RA. The control group consisted of 10 RA patients keeping their usual diet. As a result, 33 % of participants in the main group had a short-term improvement of clinical manifestations of RA and of laboratory markers of inflammation as well. In 1991 the similar study was carried out by J. Kjeldsen-Kragh et al. [50]: its 1st stage was 7-10-day fasting, the 2nd one — 3-5 months of veganism and gluten-free diets, then the stage of lactovegetarianism lasting up to one year. The patients in the control group kept their usual diet. As in the previous study, after period of fasting the patients noted a significant reduction of the RA manifestations, and this effect persisted in later stages. Note that the validity of the described studies' results is decreased by both non-representativeness of samples and non-compliance with current principles of RA patients management.

Finally in 2001 H. Müller et al. [67] published their systematic review dedicated to the effect of fasting and follow vegetarian diet on the outcomes in RA. They confirmed a small positive effect of fasting, lasting no more than 2 weeks, in relation to the severity of joint pain.

Mediterranean diet and its modification. Often referred is the study on the Mediterranean diet's effect

on RA activity conducted by L. Skldstam et al. (2003) [68]. In the patients who fed on this system for 12 weeks, a tendency to a decrease in RA activity was observed, but the effect was not statistically significant and was inferior to basic therapy. In the next 15 years, the results of 4 smaller controlled studies, their systematic review and meta-analysis carried out by C. Forsyth et al. (2018) were obtained [3]. Wherein, 2 interventional studies have proven the positive effect of the Mediterranean diet on both pain severity and disease-related quality of life; one more study has proven its effect on RA activity (i.e. decrease in DAS28 score). The authors of the review concluded that the benefit of the Mediterranean diet with RA is to reduce pain and to improve function.

According to the others [5, 20], it is use of individual components of the Mediterranean diet, which improves outcomes in RA. In 2018, the results of 3 controlled trials on this topic were analyzed: it has been revealed an inverse correlation between RA activity and both fish intake [69] and monounsaturated fatty acids daily intake [70]. The review of S. Petersson et al. (2018) [6] contains a conclusion about «small number of the studies on the effects of the Mediterranean diet in RA» and presence of «more evidence of better quality» of the beneficial clinical effects of the PUFAs supplementation. This conclusion is consonant with the opinion of G. Keyßer (2018) [5], E. Philippou et al. (2018) [7] and others.

The past 2018 year is interesting in the publication of a number of non-systematic reviews conducted by: 1) E. Philippou et al. — to present evidence of the role of nutrition in the onset of RA «and provide nutritional recommendations for reducing RA risk in susceptible individuals» [7]; 2) Y. Grygielska et al. — on the impact of nutrition, nicotine and alcohol on RA [4]; 3) K. Masuko — «to focus current findings regarding the suggested relationship between diet-derived carbohydrate, gut microbiota, and the pathogenesis of RA» [16].

Speaking on the «undefined modulating effect of nutrition» and increased risk of developing CVD in RA, K. Masuko (2018) [16] has noted the need to study the effects of **low-carbohydrate diet** in RA patients and proposed advising them a «**balanced diet** that includes appropriate amounts of carbohydrates, especially dietary fiber, ... important for maintaining the symbiosis of intestinal flora, which could be beneficial for preventing autoimmunity». The scheme of the interaction between diet, gut dysbiosis, and immune responses in RA is presented in Fig. 1. It is known that nutrition and other external factors (smoking, phycho-emotional stress, drug use) affect the components of gut microbiota, which in turn modulates local and systemic immune responses. Insufficient or inadequate nutrition or carbohydrate intake (as a source of energy and fibers) can indirectly through a microbiota affect the level of

physical activity, metabolism and immunity that lead to the development of insulin resistance, sarcopenia, obesity or cachexia in RA.

Increasing interest is **a disease-modifying potential of diet**. There has been research data on oral cavity and gut microbiota influence on protein citrullin obtained [11], as well as on a *Prevotella* enterotype dominance in case of a higher carbohydrate intake [71]. Namely this species is speculated to play a significant role in the pathogenesis of RA [72], and the reported protective effect of omega-3 PUFAs use may depend on the suppression of *Prevotella*-induced inflammation [73]. On the contrary, a higher intake of animal proteins and saturated fat is associated with a dominance of *Bacteroides* species in gut microbiota [16].

According the information analysis, in recent years, scientists have focused on assessing disease-modifying potential of the Mediterranean and vegetarian diets, in RA, of polyphenols and omega-3 PUFAs use as well. However, significant effect of these diets and supplements has not been proven. Argue that RA patients should be advised to follow a certain diet is a high risk of developing metabolic syndrome (due to low physical activity, increased catabolism, fat accumulation, development of sarcopenia and rheumatoid cachexia, and in connection with persistent inflammation and elevated level of anti-inflammatory cytokines). The use of basic antirheumatic drugs can significantly reduce this risk, but even if the medications are effective, the use of an appropriate diet should be considered.

Speaking on practical nutritional recommendations, the experts advise taking into account difficulties, which some patients with RA have in cooking and eating because of pain and limitations in their movement.

Dietary supplements with RA. Use of such supplements is common and considered to be a part of healthy life style, and even the development of cases of cancer in older women who participated in the IWHs has not affected it for 19-years observation [22]. As stated above, of particular interest are the effects of taking the omega-3 PUFAs in patients with rheumatic diseases. With RA, their evidence base is 3 systematic reviews with meta-analysis [74-76].

Intake of the essential long-chain omega-3 PUFAs — DHA (docosahexaenoic, or cervonic acid) and EPA (eicosapentaenoic, or timnodonic acid as well) — is necessary for a synthesis of anti-inflammatory substances. With rheumatic diseases, the effect of these acids is realized via peroxidase proliferator activator receptors [16, 77] and suppression of *Prevotella*-induced inflammation [73].

DHA is found in most animal tissues; it is the fat of salmon and Atlantic herring, zooplankton, marine mollusks and microalgae contain DHA in large quantities. High content of EPA have fat sea fish (herring, mackerel, salmon), sardines, cod liver, marine mollusks and breast milk. It is known that consuming fish can not en-

sure the supply of these PUFAs in an amount sufficient to have a therapeutic effect; so, they are usually taken in the form of fish oil capsules. The other source of DHA and EPA is nuts, vegetable oils and seeds [78-79].

Effectiveness of taking DHA/EPA in dose of $\geq 2,7$ g/day for 3-6 months has been proven by R.G. Goldberg et al. (2007) [74] in their Cochrane meta-analysis of 17 studies with total amount of 823 participated RA patients. The positive effect of supplementation these PUFAs was a reduction of morning stiffness and of need to use non-steroidal anti-inflammatory drugs (NSAIDs).

NSAID-saving effect of omega-3 PUFAs taken in dose of $\geq 2,7$ g/day for at least 3 months has been confirmed in the meta-analysis of Y.H. Lee et al. (2012) [75]; its primary sources were 10 RCTs — all homogenous. It is worth noting low power of this meta-analysis (in general, 183 RA patients took supplements of omega-3 PUFAs, 187 — placebo), as well as selection of primary sources from only 2 computer databases of EBM (MEDLINE and CENTRAL), besides, lack of proven effect of taking omega-3 PUFAs on morning stiffness, number of painful and swollen joints and function, too.

In 2015 S.M. Proudman et al. [80] evaluated the effects of taking different doses of omega-3 PUFAs in

RA, namely of high ($>5,5$ g/day) and low (0,4 g/day) ones. The number of patients who achieved remission or «no need to escalate therapy» turned out to be much greater in those who took high doses.

In 2018 A. Gioxari et al. [76] published the systematic and meta-analysis of the outcomes of using omega-3 PUFAs in RA patients. The results of 20 primary RCTs selected in PubMed, EMBASE and Scopus shown the effectiveness of 3-month oral intake of these acids or fish oil (as their source) in relation to both decreasing level of disease activity markers and improvement of lipid profile. This study differs from the meta-analysis of Y.H. Lee et al. (2012) not only search resources, but also more power: it included 717 RA patients who used omega-3 PUFAs and 535 patients who used [placebo]. As a result, A. Gioxari et al. have first proven the beneficial effect of adding omega-3 PUFAs on lipid profile and level of leucotriene B4 in RA patients, besides, the effect of taking these acids on the laboratory markers of RA activity has been also confirmed despite the «generally poor quality of evidence».

Both statistical significance and consistency of evidence of anti-inflammatory and metabolic effects of additional intake of omega-3 PUFAs in RA are criticized [5, 16, 80]; the experts recognize the need for pla-

Figure 1. The interaction between diet, gut dysbiosis, and immune responses in rheumatoid arthritis (by K. Masuko, 2018 [16]). Th17 – T17-helpers; Treg – regulatory T-cells; HLA – human leucocyte antigen.

cebo-controlled RCTs. They also pay attention to the fact that long-term intake of high doses of PUFAs in RA patients may be accompanied by the development of bleeding, and excessive fat intake — by an increase in calories and imbalances in the diet, which can affect the immune responses and important health outcomes.

Talking about the limited prospects for the production of fish oil capsules as sources of high doses of omega-3 PUFAs, including for effective adjuvant therapy in rheumatology, we quote G. Keyßer (2018): «Under conditions of overfishing ocean fish, an environmentally acceptable alternative is to use other resources of PUFAs» [5], namely purified lipid extracts of mollusks and vegetable oils.

Microelements, vitamins, antioxidants. Considering the high probability of developing iron deficiency with RA, several authors [5, 81-81] have noted a necessity of sufficient intake of iron from food in this disease. In spite of high prevalence of selenium and zinc deficiency with RA, no positive effect of these microelements' adding on the disease activity has been proven. Disappointing are the results of the studies on effects of complex dietary supplements containing quercetin, alfa-lipoic acid, linolenic acid, vitamin C, iron, selenium and zinc: their intake did not influence upon such markers of RA activity as the number of painful and swollen joints and the level of C-reactive protein (CRP).

Should also be remembered that use of vitamins and microelements in patients with RA can be associated with the increased risk of developing serious side effects. Besides the results of IWHS, the result of the meta-analysis of E.R. Miller et al. (2005) [83] of 19 studies dedicated to the effects of vitamin E supplements is also known: it has been proven the increase of all-cause mortality when used in doses ≥ 150 IU/day. As for vitamin D, G. Keyßer (2018) considered its addition «is indisputably necessary ... in accordance with the existing recommendations on prevention and treatment of osteoporosis» [5]. It is known that the risk of developing osteoporosis and its complications is increased with RA and other systemic rheumatic diseases, like the risk of developing iron deficiency as well.

Taking into account the fact that the associations between serum vitamin D level and presence and activity of some rheumatic diseases were proven mostly in the observational studies, A.S. Franco et al. (2017) [84] have first conducted the systematic review of the appropriate RCTs. Searching RCTs in which vitamin D or its analogues had been used with rheumatic diseases for ≥ 3 months was conducted in the main computer databases of EBM (i.e. Cochrane library, MEDLINE, EMBASE) and in the LILACS and CINAHL as well. From 668 primary sources, selected were 9 RCTs, among them 5 dedicated to the effects of vitamin D with RA, 3 — with SLE, 1 — with systemic sclerosis; the meta-analysis included 7 of them. The meta-analysis has proven the

favorable influence of sufficient intake of vitamin D on the specific antibodies' level in SLE and probably on the recurrence rate in RA. With RA, the supplementation of vitamin D was followed by slight reduction of the recurrence rate (risk difference -0,10; 95 % CI from -0,21 to 0,00), but this intervention did not affect either severity of pain or DAS28 score. With SLE, vitamin D intake was associated with significant decreasing anti-dsDNA antibodies' level (risk difference -0,10; 95 % CI from -0,18 to -0,03). The authors consider it necessary to confirm and to assess these and other effects of vitamin D with the rheumatic diseases in the further studies.

Gout. In the last decade, the evidence of the influence of both alcohol consumption and soft drink intake on the risk of developing gout is obtained. Effects of the alcohol consumption assessed earlier in the observational studies were heterogeneous. In 2013, M. Wang et al. [85] published the meta-analysis of 17 studies (a total amount of the participants 42924) proving a double increased risk of developing gout in those who use high doses of alcohol when compared with the teetotalers and those who drink alcohol rarely (RR=1,98; 95 % CI 1,52-2,58). The table 2 shows a dose-dependency of this effect. Namely this meta-analysis has confirmed that the alcohol consumption is a risk factor of developing gout. It is worth note that low to moderate alcohol intake has no protective effect on the developing gout (as opposed to both RA and SLE).

The evidence established in Canada by H.K. Choi et al. (2007) [86] is also of interest. For 12 years they have prospectively observed the cohort of 45869 men not suffering on gout at baseline; the consumption of coffee, decaffeinated coffee, tea and caffeine was assessed every 4 years using the FFQ questionnaires. During the period of the study the diagnosis of gout was established in 757 (1,7 %) participants. The results confirmed the beneficial effect of prolonged coffee consumption (in doses of ≥ 4 cups/day, and decaffeinated — in doses of 1-3 cups/day) in relation to the risk of developing gout. Such indicators of RR were calculated: when coffee was not used — 1,00, when it was used in dose < 1 cups/day — 0,97, when 1-3 cups/day — 0,92, when 4-5 cups/day — 0,60 (95 % CI 0,41-0,87), when > 6 cups/day — 0,41 (95 % CI 0,19-0,88). The indicators of RR of developing gout depending on the daily dose of use of decaffeinated coffee: when it was not used — 1,00, when it was used in dose < 1 cups/day — 0,83, when 1-3 cups/day — 0,67 (95 % CI 0,54-0,82), when ≥ 4 cups/day — 0,73 (95 % CI 0,46-1,17). Like with RA [32], total caffeine intake did not influence on the risk of developing gout.

The basis of management of the patients with gout according to the recommendations of the European League Against Rheumatism (EULAR, 2006), American College of Rheumatology (ACR, 2012), Deutsche Gesellschaft für Allgemeinmedizin und Familienmedi-

zin (DEGAM, 2009), Deutsche Gesellschaft für Rheumatologie (DGRh, 2017) etc. is a lifestyle modification which potentially provide a decrease of serum uric acid (sUA) level by 10–15%. The lifestyle modification suggest modification of pharmacotherapy (i.e. cancelling diuretics, salicylates, cyclosporin A, beta-blockers; preferred use of losartan, fenofibrate, calcium channel blockers), dietary modification (restriction of the use of foods rich in purines, — fried meat, sprat, herring, sardines, sole, beer and other alcohol and fructose-containing soft drinks; increasing of use of dairy products, cherry, coffee, and vitamin C), as well as sufficient consumption of liquid, slow weight loss and moderate physical activity. However, in 2017 the DGRh experts confirmed the lack of studies on the effects of both meat and alcohol intake in the population of the patients with gout [87].

Our information analysis shows that the effects of the lifestyle modification with gout have been studied in three Cochrane systematic reviews [88–90].

In the review of J.H. Moi et al. (2013) [88] the effects of the interventions on lifestyle changes have been first studied. The search of the primary sources was conducted by the authors in the main computer databases of EBM (CENTRAL, MEDLINE and EMBASE; up to 05.04.2013) and in the abstracts of the EULAR and the ACR of 2010–2011. Selected were the RCTs and the quasi-randomized trials in which the effects of the lifestyle changes had been compared to the other treatment (active or placebo). It was planned the assessment of the influence of the interventions on the following outcomes: rate of gouty attacks, severity of joint pain, level of sUA, size of tophi, joint function, quality of life, adverse effects (AEs). As a result, the systematic review included the only RCT (120 male-participants aged 50–60 years with severe gout; the risk of bias was assessed as «moderate»). For three months, the patients of the main group delivered skimmed milk powder enriched with glycomacropeptide SMP/GMP/G600, while the patients of two control groups used raw milk powder or lactose powder. As the results: 1) the rate of gouty attacks and the severity of joint pain have decreased in each group; 2) «the evidence of low quality» has proven similarity of the groups with respect to the development of AEs — most often these were gastrointestinal, including those resulting in hospitalization. The effects of the interventions on the sUA level, tophi size, joint function and quality of life had not been reported in this

RCT. The authors of the review highlighted the lack of the best evidence from the RCTs for supporting or rejecting lifestyle changes with gout, despite having good evidence from the observational studies for linking various lifestyle factors to the increased risk of developing gout.

Two months later the described study was included in the Cochrane review by M. Andrés et al. (2014) [89], in which the assessment of both effectiveness and safety of the dietary supplements' use in the adults patients with chronic gout has been performed. The primary sources were also selected without language restrictions from the MEDLINE, EMBASE, CINAHL and the abstracts of the EULAR and ACR (2010–2013). Selected were the RCTs and the quasi-randomized trials, in which the effect of the dietary supplements' use had been compared to no use of these supplements, use of placebo, of «other supplements» and of drugs. The dietary supplements' composition included aminoacids, antioxidants, essential minerals, PUFAs, prebiotics, probiotics, vitamins, «other substances» as well. The main endpoints were decrease of gouty attacks rate and withdrawal from the study due to the development of AEs. Such outcomes as a decrease of severity of joint pain, disease-related quality of life, normalization of the sUA level, joint function, tophi regression, and rate of the serious AEs were also taken into account.

The review included 2 RCTs: a total number of participants — 160, including 120 those who took part in the above-mentioned RCT of the effects of skimmed milk powder enriched with glycomacropeptide and 40 participants of the RCT of the effects of vitamin C alone compared with allopurinol and with allopurinol plus vitamin C. These studies differed in validity (in the second the sample was less, but its representativeness was better, the risk of bias was greater) and in major endpoints (in the second it was level of sUA). The results of the second RCT shown, that vitamin C did not lower sUA as much as allopurinol (low-quality evidence), and good tolerance of this supplement as well. M. Andrés et al. concluded: «While dietary supplements may be widely used for gout, this review has shown a paucity of high-quality evidence assessing dietary supplementation».

The beneficial and adverse effects of weight loss for overweight and obese patients with gout were evaluated in the Cochrane review conducted by S.M. Nielsen et al. (2017) [90]. They searched six computer databases

Table 2. Risk of gout development depending on different alcohol intake when compared with no use or rare use of alcohol (by Wang M. et al., 2013 [85])

Alcohol intake (dose/day)	Relative risk of gout development (95 % CI)
≤ 1	1,16 (1,07–1,25)
1–3	1,58 (1,50–1,66)
≥ 3	2,64 (2,26–3,09)

CI — confidence interval.

of EBM for longitudinal studies, reporting the effect of weight loss in overweight/obese gout patients, while evaluating the risk of bias and quality of evidence. As a result, from 3991 potential eligible studies, only 10 were selected, including one RCT. No intervention was compared to such interventions as diet with/without physical activity, bariatric surgery, diuretics, metformin. The analysis of the primary studies has shown, that mean weight loss in their participants ranged from 3 to 34 kg, the effect on sUA level — from 30 to 168 $\mu\text{mol/L}$, and 0-60 % patients achieving sUA target ($<360 \mu\text{mol/L}$). Fewer gout attacks following losing weight was observed in 75 % (6 out of 8) studies, while two studies revealed dose-dependence of this beneficial effect (the rate of attacks correlated with a decrease in sUA level and the achievement of the target). Temporary increased sUA level and gout attacks rate tended to occur at short term after bariatric surgery. The results of the review are: 1) the benefits of weight loss for overweight and obese patients with gout has been proven; 2) the quality of evidence has been evaluated (low — for effects on sUA and gout attacks, moderate — for achieving sUA target) as well as weakness of current evidence in general («a few studies mostly observational of low methodological quality»); 3) «an urgent need» to initiate prospective studies, preferably RCTs, has been highlighted.

So, the influence of diet quality, eating certain foods and alcohol on the risk of developing rheumatic diseases first of all is proven for RA and gout, at least — for SpA and SLE. Smoking is a strong risk factor for developing RA in predisposed individuals, and increasing this risk is associated with both excess salt intake and increased BMI. Modern science has evidence of the effect of a number of diets on outcomes in RA. Quality of most RCTs and effects of such interventions of life quality of the patients are criticized by experts who nonetheless suggest that health workers promote the Mediterranean diet in patients with RA, taking into consideration its beneficial effect on cardiovascular risk. According to G. Key et al. (2018) [5], short fasting can be recommended for overweight patients with stable course of RA. Scientifically based is the feasibility of applying a carbohydrate-balanced diet with RA, taking into account its influence on the immune and metabolic disorders and gut microbiota as well (Masuko K., 2018) [16].

Discussing the external risk factors of developing and outcomes of rheumatic diseases associated with nutrition let's move to the proven effects of **microbiota** and its correction in these diseases. It is known that both trigger and modulating role of the oral cavity and gut microbiota in the development of immune reactions is experimentally established and confirmed [9]. The attempts to use probiotics and prebiotics for adjunctive therapy in the rheumatic diseases are based namely on their immune-modulating properties [10-12].

Probiotics are living microorganisms that, when entered the body in sufficient quantities, have benefi-

cial health effects. Lactobacilli are applied longer than other microbes (they have greater evidence base in RA, too), while bifidobacteria, *B. clausii*, yeast are also used. There are several forms of application of probiotics: 1) as part of food enriched with them; 2) as dietary supplements; 3) as drugs.

The scientific research of probiotics' effects in chronic inflammatory diseases have been conducted since the association of RA, SpA and other rheumatic diseases with pathological changes of gut microbiome became apparent [10, 15, 91-92]. Gut microbiome is considered significant in the pathogenesis of SLE, Sjogren syndrome [13] and gout as well [93].

Noting almost universal (in the USA, China and Finland) prevalence of gut dysbiosis in patients with RA, Y. Maeda et al. (2016) [9] suggest, that the results of modern laboratory studies of probiotics' and prebiotics' use «give hope for new therapeutical and preventive strategy» in this disease. This hypothesis is supported by Y. Kang et al. (2017) [10]: «Oral intake of probiotics/prebiotics can therefore represent a therapeutic approach for RA treatment. However, the relevant scientific work has only just begun, and the available data in this field remain limited». The evidence base of the effects of probiotics' use in RA is described by A. Schorpion et al. (2017) [11]: «Clinical trials to date have been small and mostly short term ... endpoints have varied from study to study and have been of limited clinical significance...There remain theoretical reasons to further investigate the use of probiotics as adjunctive therapies for autoimmune disease...».

With SpA, the effects of use of probiotics have been assessed by K. Jenks et al. (2010) [94] in the small placebo-controlled RCT (63 participants) conducted in New Zealand. The scales BASDAI, BASFI, MASES, ASAS, ASQoL and DISQ were applied; no positive effect of use of *Streptococcus salivarius*, *Bifidobacterium lactis* and *Lactobacillus acidophilus* has been proven.

With other rheumatic diseases, the clinical trials on the probiotics' effects were also carried out in the last decade, but most of the evidence relates namely to RA [95-100] and the effects are ambiguous.

In particular, in 2011 L. Pineda Mde et al. (Canada) [95] presented the results of the pilot 3-month double blind placebo-controlled RCT, whose participants were 29 patients with stable RA who did not take glucocorticoids during the study and a month before. Among them, 15 patients took orally capsules containing *L. rhamnosus GR-1* and *L. reuteri RC-14*; the control group included 14 patients. This control group shown more significant changes of cytokines level; effect of use of probiotic was comparable to placebo and consisted of improving both functional status and life quality (assessed with HAQ).

In 2014, the encouraging results of using probiotic as adjunctive therapy for RA were obtained in Iran [96-97] — as a result of 8-week double blind placebo-con-

trolled RCT of effects of oral taking capsules containing *L. casei* 01 in a daily dose of at least 10^8 colony forming units (CFU/day). Investigated were 46 women aged 20-80 years with BMI <40 kg/m² and diagnosis of RA established not earlier than one year before, with stable course of the disease for at least 3 months prior to enrollment. The patients in the main group took capsules containing *L. casei* 01. as a result, they revealed more significant reduction of disease activity score (DAS28) and more pronounced favorable change in the profile of cytokines (decrease of tumor necrosis factor alfa (TNF α) and interleukin (IL) IL-6 and IL-12, but not IL-1 β levels in blood; increase of IL-10 level and IL-10/IL-12 ratio) when compared with the results in the placebo group (i.e. taking capsules filled with maltodextrin).

The work of other Iranian scientists B. Zamani et al. (2016) [98] contains an assessment of probiotics' effects on both clinical and metabolic status of patients with RA: 60 patients aged 25-70 years participated in 8-week double blind placebo-controlled RCT. The patients in the main group took orally capsules containing 3 live lyophilized strains of lactobacteria and bifidobacteria — *L. acidophilus*, *L. casei* and *B. bifidum*, each of them in a dose of $2 \cdot 10^9$ CFU/day. The patients in the control group took capsules filled with cellulose. The results have shown the effectiveness of this multicomponent probiotic's use in the complex treatment of patients with RA: when compared with the control group, they revealed more significant reduction of both scores — DAS28 and HOMA-B (homeostatic model assessment B-cell function), as well as of blood levels of insulin and high-sensitive C-reactive protein (hs-CRP).

Reduction of hs-CRP level in patients with RA treated with oral capsules containing monocomponent probiotic *L. casei* has been earlier established by B. Alipour et al. (2014) [96]. They concluded that clinical significance of these metabolic effects required clarification in further clinical trials.

Finally, effectiveness of probiotics as adjunctive therapy in RA was assessed by A.T. Mohammed et al. (2017) in their systematic review and meta-analysis [99]. The sources of evidence were 9 primary studies (total number of participants — 361) selected from 9 computer databases of EBM. It has been shown, that the patients treated with probiotics have lower blood level of IL-6 when compared with placebo-treated patients, but there is no difference between the groups in the disease activity score DAS28. The authors concluded that it is necessary to conduct new studies on effects of probiotics to confirm their clinical significance.

Somewhat different results shown S.M. Aqaeinezhad Rudbane et al. (2018) [100] in the meta-analysis of 4 RCTs, which aim was also to compare the effects of probiotics and placebo in RA. The total cohort consisted of 153 participants, most women (89 %). Taking probiotic did not affect neither erythrocyte sedimentation

rate (ESR) nor pro-inflammatory cytokines' (TNF α , IL-1 β , IL-6, IL-12) and oxidative stress markers' (total antioxidant capacity, malondialdehyde) levels, but followed by reducing both CRP level and DAS28 score. The authors noted small number of sources of the meta-analysis that did not allow to confirm dependence of effects of probiotics on their composition, dose or duration of use; although the effectiveness of taking probiotics in RA was assessed as insignificant.

So, a number of clinical trials conducted in Canada, New Zealand and Iran with the aim of assessing anti-inflammatory effects of probiotics in rheumatic diseases gave disappointing results. In patients with SpA, the multicomponent probiotic turned out to be ineffective; in patients with RA, use of lactobacilli did not lead to clinical improvement.

It is worth noting, that in 2012 F.A. Mendoza et al. [101] described two cases of developing severe eosinophilic muscle syndrome in chronological connection with taking probiotic. An alternative opinion of A.C. Ouwehand et al. on suggested trigger role of probiotic was published in 2013 — along with the call for rigorous quality control and careful monitoring of tolerability of probiotics in «severely immune-compromised patients» that may have increased risk of developing adverse effects [102].

No such and other side effects of probiotics in rheumatic patients were in the above-mentioned studies observed.

Conclusions

1. The importance of nutrition in terms of the risk of developing rheumatic diseases and primarily RA has been proven by evidence from some large cohort studies conducted first of all in the USA. Their results have confirmed protective potential of long-lasting breastfeeding, as well as of safe (adequate) nutrition in childhood and healthy nutrition in adulthood — along with the benefits of full and as early as possible smoking cessation as the most effective technology of primary prevention of RA. Recently, no large RCTs on the effect of nutrition on disease activity degree and other outcomes in RA have been carried out, but several small observational studies have been conducted.

2. Tobacco use is a strong risk factor of developing RA during the lifetime in predisposed individuals, has the strongest evidence base among all external factors, and should be taken into consideration as a confounding factor while planning, conducting and assessing the results of any studies dedicated to effect of nutrition in this disease. Increased risk of developing RA in smokers is associated with both excess salt intake and increased body mass index. The effects of smoking can be mediated by its influence on gut microbiome — along with the influence of psycho-emotional stress, nutrition and drug use.

3. The role of alcohol as a risk factor for disease's development and outcomes has been confirmed first of

all in RA (it means protective effect of low to moderate alcohol consumption and unfavorable effect of alcohol abuse) as well as in gout (unfavorable dose-dependent effect). Moderate alcohol intake can reduce the risk of developing SLE in women. It is eating oily marine fish and citrus, as well as avoiding sweet soft drinks at a young age that may have a protective effect on the onset of RA symptoms. The effects of coffee intake in terms of the risk of developing gout (protective) and the effects of drinking both coffee and tea in terms of the risk of developing RA (ambiguous) are apparently not related to the caffeine content in these products.

4. The inconsistency of evidence of protective effect of the use of some foods and ingredients (such as alcohol, salt, fish, unrefined olive oil, vegetables) and of negative effect of other ones (red meat, sweet soft drinks) in terms of the risk of the developing RA has been explained by the possibility of realizing these effects only with a combination of nutritional factors, adherence to a certain diet pattern, and so on. Both preventive potential and safety of the dietary supplements are to be further evaluated in the studies; a possible slight reduction of the risk of developing RA has been revealed only by using zinc and beta-cryptoxanthin supplements.

5. The potential benefits of a Mediterranean diet for the primary prevention of rheumatic diseases are related to its beneficial effect on the risk of developing metabolic syndrome and CVD. The results of 2 systematic reviews conducted in 2018 show weakness of evidence supporting such nutrition as technology of primary prevention of RA; they also allow to propose hypothesis of greater effectiveness of the modified Mediterranean diet — with increased consumption of fatty fish, low intake of sugar, and maintaining normal body weight.

6. Current evidence of the effects of the various diets' use in RA is of low quality and does not compete with evidence of pharmacotherapy. The benefits of the Mediterranean diet, proven recently in the systematic review, are both reducing pain and functional improvement. The disease-modifying potential of this diet in RA has not been confirmed (like of vegetarianism and adding of polyphenols or omega-3 PUFAs), but it is supposed an expediency of combination of effective basic therapy «with appropriate diet» (it may be a balanced carbohydrate intake) in order to reduce the risk of developing metabolic syndrome. This hypothesis is to be proven in epidemiological studies.

7. With gout, three recent Cochrane reviews have provided only weak evidence of effects of such interventions as dietary modifications and supplements' use, as well as of benefits of reducing weight in overweight and obesity. The conclusions of these reviews encourage strengthening evidence of the mentioned factors in gout by conducting relevant RCTs of high methodological quality.

8. The attempts to use vitamins, minerals and other dietary supplements in the treatment of patients with

rheumatic diseases continue. The systematic reviews and meta-analysis have proven favorable effects only for fish oil capsules containing high doses of omega-3 PUFAs ($\geq 2,7$ g/daily) — in RA (i.e. reduction the need for NSAIDs and reduction of disease activity), as well as for sufficient use of vitamin D — in SLE (i.e. reduction of specific antibodies) and RA (i.e. recurrence rate reduction). Taking into account the risk of developing adverse effects, the use of iron- and vitamin D-containing supplements in patients with rheumatic diseases should strictly comply with the available recommendations.

9. Scientific interest in pathogenetically justified use of probiotics in rheumatological practice, which has increased in recent years, has been realized in a few controlled trials of their effects in RA (on the example of lactobacilli supplements), and no convincing evidence of their effectiveness has been received. Continuation of research in this direction is considered promising. Sufficient evidence will allow to confirm or refute the hypothesis about the expediency of use of probiotics in patients with RA and other rheumatic diseases and justify the new strategy of their management.

10. Research of nutritional effects in rheumatic diseases is still relevant. Development of special recommendations on nutrition in rheumatic diseases is a promising scientific task. For today, practically significant is such a component of patient management as preventive counseling on nutrition with the aim of reducing cardiovascular risk.

Conflicts of interests. Author declares the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Харчування як чинник ризику та втручання при ревматичних захворюваннях

Резюме. Мета публікації — огляд ефектів харчування як чинника ризику та втручання в аспекті ревматичних захворювань. З використанням методів інформаційного аналізу досліджено понад 100 джерел спеціальної літератури та комп'ютерних ресурсів доказової медицини. У великих обсерваційних дослідженнях, систематичних оглядах і мета-аналізах, присвячених профілактичному, терапевтичному потенціалу та безпеці застосування різних харчових продуктів, дієт, мікронутрієнтів і пробіотиків, у тому числі за наявності пов'язаних провідних чинників ризику неінфекційних захворювань (вживання тютюну, алкоголю, підвищеного індексу маси тіла тощо), встановлено, що значущість харчування як чинника ризику розвитку та кінцевих результатів доведено насамперед для ревматоїдного артриту та пода-

гри. Патогенетичну роль харчування розглянуто в контексті його впливу на кишкову мікробіоту. Показано необхідність проведення рандомізованих контрольованих досліджень для оцінки протективного потенціалу різних моделей харчування й ефектів дотримання модифікованої середземноморської дієти та вживання певних дієтичних добавок і пробіотиків при ревматичних захворюваннях, а в кінцевому результаті — для розробки спеціальних настанов із харчування для хворих ревматологічного профілю. Відзначено достатню доказову базу профілактичного консультування таких пацієнтів з питань харчування з метою зниження кардіоваскулярного ризику.

Ключові слова: ревматичні захворювання; харчування; чинник ризику; втручання; огляд

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Питание как фактор риска и вмешательство при ревматических заболеваниях

Резюме. Цель публикации — обзор эффектов питания как фактора риска и вмешательства в аспекте ревматических заболеваний. С применением методов информационного анализа изучено более 100 источников специальной литературы и компьютерных ресурсов доказательной медицины. В крупных обсервационных исследованиях, систематических обзорах и метаанализах, предметом которых были профилактический, терапевтический потенциал и безопасность применения различных пищевых продуктов, диет, микронутриентов и пробиотиков, в том числе в связи с сопряженными ведущими факторами риска неинфекционных заболеваний (курением, употреблением алкоголя, повышенным индексом массы тела), доказана значимость питания как фактора риска развития и исходов прежде всего ревматоидного артрита и под-

агры. Патогенетическая роль питания рассмотрена в контексте его влияния на кишечную микробиоту. Показана необходимость проведения рандомизированных контролируемых исследований для оценки протективного потенциала различных моделей питания и эффектов применения модифицированной средиземноморской диеты, ряда диетических добавок и пробиотиков при ревматических заболеваниях, а в конечном итоге — для разработки специальных рекомендаций по питанию больных ревматологического профиля. Отмечена достаточная доказательная база профилактического консультирования таких пациентов по вопросам питания с целью снижения кардиоваскулярного риска.

Ключевые слова: ревматические заболевания; питание; фактор риска; вмешательство; обзор